REMARKS

Reconsideration and allowance are respectfully requested.

Claim 69 has been amended for a better definition of the invention by reciting that:

(a) the therapeutic agent is a radio-labeled soluble precipitable material;

(b) the therapeutic material is for use as a pro-drug; and

(c) the pro-drug is converted into an insoluble and non-digestible radio-labeled precipitate.

In a telephone conference of the undersigned attorney and the Examiner on July 2, 2002, the Examiner stated that consideration should be given to claiming a therapeutic material of soluble precipitable material for use as a pro-drug.

It is submitted that Claim 69 has been amended herein to claim a therapeutic material of a soluble precipitable material for use as a pro-drug.

"Substituted indoxyl portion" is disclosd on pages 21 and 23 of the specification.

"Radio-labeling" is disclosed on page 23 of the specification.

"Killing non-selectively by immobilized isotopes" is disclosed on page 26 of the specification.

Claim 70 is distinguished by being dependent upon Claim 69.

Claims 71 and 72 have been amended to delete "cell-impermeant material" and to insert cell-impermeant chemical group. It is submitted that this amendment to claims 71 and 72 is responsive to the Examiner's rejection of Claims 71 and 72 on pages 2 and 3 of the Action.

The "chemical group" of amended Claim 71 and the "chemical groups" of amended Claim 72 are disclosed on page 19 of the specification.

Claims 73 and 74, which depend upon amended Claim 69, are distinguished similarly as Claim 69.

Amended Claim 75, which depends upon Claim 74 and thereby Claim 69, is distinguished by reciting that the extra-cellular precipitate is "radio-labeled."

Amended Claim 76, which depends upon Claim 69, is distinguished by reciting that the extra-cellular precipitate is "radio-labeled." Again, "radio-labeling" is disclosed on page 23 of the specification.

Amended Claims 77 and 78 are distinguished by reciting that the "indoxyl compound to reduce the ability of the extra-cellular radio-labeled precipitate" to move in the extra-cellular fluid. This reduction to movement is disclosed on pages 22 and 23 and 30 of the specification.

Amended Claims 79 and 80, which depend upon Claim 69, are each distinguished by reciting that the extra-cellular precipitate is "radio-labeled" as described on page 23 of the specification.

Claim 81, which depends upon Claim 80, is distinguished similarly as Claim 80.

Claim 82 has been cancelled without prejudice.

The following Remarks are wtih respect to the Action of July 5, 2002.

Paper 40, Page 3, line 17, (a')

" ... the arguments have been considered but not found persuasive (a') for the reasons previously set forth in Paper 15 ..." (Should be Paper 18)

Paper 18, Page 3-4, Line 17 (page 3) - Line 5 (page 4), (a')

" ... (a') a review of the cited support reveals general teachings of the chemistry of indoxyl chemistry but does not provide guidance on or exemplification of making or using the broadly claimed agents ... a review of the specification does not reveal the absolutely critical nature of radio-labeling of the therapeutic agent."

Response (a')

Applicant has amended claim 69 to include the term radio-labeled. The therapeutic agent claimed in the present invention is a radio-labeled soluble precipitable material for use as a pro-drug where the soluble precipitable material is converted into an insoluble and non-digestible radio-labeled precipitate by the enzyme moiety of a bispecific agent previously bound to a non-endocytosing receptor or other extra-cellular matrix generated within the tumor (such as CEA which is commonly used in ADEPT). The radio-labeled precipitate therefore being an extra-cellular radio-labeled precipitate that remains adjacent to the bound bispecific agent for an extended period of time sufficient to kill non-selectively all cells adjacent to the extra-cellular radio-labeled precipitate. Applicant believes that this change clarifies the present invention and that it overcomes the Examiner's objection that the Applicant is arguing limitations not recited in the claims as presently constituted. Support for inclusion of this change is in the specification of the present invention on page 23. In addition, FIG. 15-17 of the present invention disclose the specific case of radio-labeling an indoxyl-based compositions of the therapeutic agent.

In addition to substituted indoxyl compounds having molecular positions 1-7, the present invention describes alternate compositions for the therapeutic agent including peptides, including opio-melanins, carbohydrates including cellulose, chitosan, and chitin, proteoglycans, and synthetic polymers. The present invention provides sufficient disclosure and examples to enable one of skill in the art to make and use these broadly claimed therapeutic agents. All of these compositions are specific examples of the general example described on page 23-24:

"An additional method of converting first therapeutic agent into an insoluble material which precipitaes in the extra-cellular fluid is where the first therapeutic reagent has a soluble moiety and an insoluble moiety, the soluble moiety having a solubilizing effect on the insoluble moiety and being cleaved by the first enzyme moiety of the first bispecific reagent, the solubilizing effect of the soluble moiety being thereby dissipated and the remaining material, being insoluble, spontaneously forming a precipitate. FIG. 18 shows an specific example of this method of precipitation in which beta lactamse cleaves the bond between the soluble and insoluble moiety causing the insoluble moiety to spontaneously precipitate."

Building on this disclosure in the specification, claims, and figures of the present invention of an additional method of converting a therapeutic agent into an insoluble material, one of skill in the art could prepare a wide variety of compositions of a therapeutic agent for use in the present invention. For example, in FIG. 18 of the present invention, the use of a solublizing polymer coupled to an insoluble compound via a cephalosporanic acid coupling is disclosed. One of skill in the art would recognize that there are many different compounds available for each segment of the therapeutic agent -- the choice of solubilizing polymer (e.g. PEG), the choice insoluble compound (e.g. hydrophobic HPMA, polystyrene, etc.) and the choice of the enzyme sensitive coupling (e.g. ester linkage breaks OH of PEG). To one of skill in the art, the synthesis and radio-labeling of such agents is straightforward organic chemistry and could be achieved using a variety of published methods including iodination (as described in the specification on page 23), attachment of an iodo-benzene, attachment of chelating agent, etc.

In addition, one of skill in the art would be able to prepare a therapeutic agent by coupling through an enzyme-sensitive linkage two different polymers – one that would provide the solublizing function, and the second that is inherently insoluble and that would precipitate after the coupling linkage was broken.

In addition, one of skill in the art would be aware that the therapeutic agent disclosed in the present invention could also be prepared using certain peptides such as prion proteins, amyloid of Alzheimer's disease, and keratins which are all known to be quite non-degradable. In the case of the named opio-melanins, although the peptide portion may be degradable, the remaining melanin portion is quite non-degradable.

The present invention provides sufficient disclosure to enable one of skill in the art to use of any of the radio-labeled therapeutic agents disclosed in the present invention in the disclosed method for therapy of cancer. Using the dose data for bispecific agents disclosed references cited in the specification on page 9 for ADEPT (which we also sent to the Examiner), one of skill in the art would be able to estimate accurately the enzyme concentration in various tumors and therefore, knowing the turnover rate of the enzyme, would be able to accurately dose the patient using any of the radio-labeled therapeutic agents disclosed in the present invention to achieve a therapeutic radiation dose to the tumor.

See also Mayers Declaration of January 2, 2003.

Paper 40, Page 3, Line 18-19, (b')

"... (b') the arguments have been considered but not been found persuasive for the reasons previously set forth in Paper No. 27."

Paper 27, page 4, line 14-15, (b')

"... (b') Applicant is arguing limitations not present in the claims as currently constituted as immobilization of a radio-isotope is not claimed."

Response (b'):

Applicant has amended claim 69 to include the term radio-labeled. Applicant believes that this change clarifies the present invention and that overcomes the Examiner's objection that the Applicant is arguing limitations not recited in the claims as presently constituted (see a' above). Support for inclusion of this change is in the specification of the present invention on page 23. In addition, FIG. 15-17 of the present invention disclose the specific case of radio-labeling an indoxyl-based compositions of the therapeutic agent.

In the present invention, the radio-labeled therapeutic agent is converted into an insoluble radio-labeled precipitate via the action of the enzyme moiety of the bispecific reagent that was previously bound to the non-endocytosing receptors of cancer cells. The conversion of a radio-labeled therapeutic agent results in the formation of a radio-labeled extra-cellular precipitate and

thereby achieves the immobilization of isotopes throughout the tumor sufficient to kill non-selectively all cells adjacent to the extra-cellular radio-labeled precipitate.

This is the crux of the patent and what is meant by a radio-labeled soluble precipitable reagent. When it is injected into the person it is soluble and can circulate through the body, but when it comes in contact within the tumor with the enzyme that has been previously placed within that tumor, the soluble precipitable reagent is converted into a radio-labeled precipitate thereby immobilizing the isotope as part of that precipitate within the tumor and acting as a therapeutic agent. That portion of the reagent that is not so converted is to be quickly excreted in the urine to limit any toxicity outside the tumor.

See also Mayers Declaration of January 2, 2003.

Paper 40, Page 3, Line 20-22, (c')

"...(c') Applicant is arguing limitations not recited in the claims as bispecific reagent is not being claimed, only a therapeutic agent being a soluble precipitable material is claimed."

Paper 27, Page 4, Line 14-17, (c')

"...(c') Applicant is claiming a therapeutic agent ... Applicant admits on the record that the claimed therapeutic agent is not therapeutic *per se.*"

Response (c'):

Applicant has amended claim 69 to include the term radio-labeled. Applicant believes that this change clarifies the present invention and that overcomes the Examiner's objection that the Applicant is arguing limitations not recited in the claims as presently constituted (see a' above). Support for inclusion of this change is in the specification of the present invention on page 23. In addition, FIG. 15-17 of the present invention disclose the specific case of radio-labeling an indoxyl-based compositions of the therapeutic agent.

In the present invention, the radio-labeled therapeutic agent is converted into an insoluble radio-labeled precipitate via the action of the enzyme moiety of the bispecific reagent that was

previously bound to the non-endocytosing receptors of cancer cells. The conversion of a radio-labeled therapeutic agent results in the formation of a radio-labeled extra-cellular precipitate and thereby achieves the immobilization of isotopes throughout the tumor sufficient to kill non-selectively all cells adjacent to the extra-cellular radio-labeled precipitate.

See also Mayers Declaration of January 2, 2003.

Paper 40, Page 3, Line 22-23, (d')

"...(d') The arguments have been fully considered and are not persuasive for the reasons previously set forth."

Paper 40, Page 3, Line 23, (f')

"...(f') The arguments have been fully considered and are not persuasive for the reasons previously set forth in Paper 33."

Paper 33, Page 4, Line 12-15, (d')-(f')

"...(d')-(f') Applicant is arguing limitations not recited in the claims as presently constituted ... is not therapeutic."

Response (d')-(f'):

Applicant has amended claim 69 to include the term radio-labeled. Applicant believes that this change clarifies the present invention and that overcomes the Examiner's objection that the Applicant is arguing limitations not recited in the claims as presently constituted (see a' above). Support for inclusion of this change is in the specification of the present invention on page 23. In addition, FIG. 15-17 of the present invention disclose the specific case of radio-labeling an indoxyl-based compositions of the therapeutic agent.

In the present invention, the radio-labeled therapeutic agent is converted into an insoluble radio-labeled precipitate via the action of the enzyme moiety of the bispecific reagent that was previously bound to the non-endocytosing receptors of cancer cells. The conversion of a radio-labeled therapeutic agent results in the formation of a radio-labeled extra-cellular precipitate and

thereby achieves the immobilization of isotopes throughout the tumor sufficient to kill non-selectively all cells adjacent to the extra-cellular radio-labeled precipitate.

See also Mayers Declaration of January 2, 2003.

Paper 40, Page 4, Line 1-3, (e'), (g'), (h')

"...(e'), (g'), (h') the arguments are not persuasive for the reasons previously set forth in Papers Nos. 15 and 27."

Paper 27, Page 4-5, Line 19-23 (p. 4) – Line 2 (p.5), (e')

"...(e') it is clear that the limitation that the therapeutic agent ... other than claim 83, none of the claims are drawn to a radio-label soluble precipitable material and none of the claims are drawn to immobilized reagents ...not predict that the only location where the therapeutic agent will be immobilized will be at the site of the bispecific reagent."

Paper 18, Page 4, Line 19-22, (e')

"... (e') ... the therapeutic agents may be inactivated *in vivo* ... rejection is maintained."

Response (e'):

Applicant has amended claim 69 to include the term radio-labeled. Applicant believes that this change clarifies the present invention and that overcomes the Examiner's objection that the Applicant is arguing limitations not recited in the claims as presently constituted (see a' above). Support for inclusion of this change is in the specification of the present invention on page 23. In addition, FIG. 15-17 of the present invention disclose the specific case of radio-labeling an indoxyl-based compositions of the therapeutic agent.

In the present invention, the radio-labeled therapeutic agent is converted into an insoluble radio-labeled precipitate via the action of the enzyme moiety of the bispecific reagent that was previously bound to the non-endocytosing receptors of cancer cells. The conversion of a radio-labeled therapeutic agent results in the formation of a radio-labeled extra-cellular precipitate and

thereby achieves the immobilization of isotopes throughout the tumor sufficient to kill non-selectively all cells adjacent to the extra-cellular radio-labeled precipitate.

Regarding the location where the radio-labeled therapeutic agent will be immobilized, as disclosed in the claims and specification of the present invention (Specification, page 17, 19-24), the conversion of the radio-labeled therapeutic agent can only occur via the action of the non-mammalian enzyme moiety of the bispecific reagent. The conversion of the radio-labeled therapeutic agent into the insoluble extracellular radio-labeled precipitate by the enzyme moiety of the previously bound first bispecific reagent is analogous to the prior art of ADEPT wherein a soluble prodrug is converted by the enzyme moiety of a previously bound bispecific reagent into an active drug (Specification, p. 9-10 and Publication Exhibits for ADEPT (A and G-J) submitted with the response filed May 25, 1999, page 36). Just as the pro-drugs of ADEPT are adapted to be converted to active drugs only by the enzyme moiety of the previously bound bispecific reagent, so the therapeutic agent of the present invention is adapted to be converted to the first extra-cellular precipitate only by the non-mammalian enzyme moiety of the previously bound first bispecific reagent.

As disclosed in the specification of the present invention, the therapeutic agent can be prepared with a variety of chemical linkages that are sensitive only to non-mammalian enzymes and therefore will not be cleaved by any of the naturally occurring enzymes in the living host. For example, the present invention describes different indoxyl preparations that will only undergo conversion to their insoluble form via the action of be non-mammalian enzymes such as lactamases, beta-lactamases, phosphatses, chondroitinases, and the like (Specification p. 20-21, 22-23, and 33). In additionThe disclosure in the present invention enables one of skill in the art to recognize that because such enzymes are not normally present in the living host except as the enzyme moiety of the previously bound bispecific reagent, that the conversion of the soluble radio-labeled therapeutic agent into the radio-labeled precipitate would only occur in the cancer at the site of the bound bispecific reagent.

See also Mayers Declaration of January 2, 2003.

Paper 40, Page 4, Line 1-3, (e'), (g'), (h')

"...(e'), (g'), (h') the arguments are not persuasive for the reasons previously set forth in Papers Nos. 15 and 27."

Paper 27, page 5, line 6-10, (g')

"... (g') Applicant was invited to submit objective evidence to resolve this issue, no objective evidence has been submitted but Applicant has admitted on the record that 'ultimately, the insoluble precipitate will be removed by convection and phagocytosis but such removal from tumor tissue will be slower than for normal tissues.'"

Paper 27, page 5, line 23 – page 6, line 7

"Dr. Epstein states that insoluble DNA is retained much longer in tumor tissue compared to normal tissue and that one skilled in the art would readily recognize that the insoluble precipitate formed in Dr. Rose's invention will be retained in the same way. The argument has been considered but has not been found persuasive because it is clear that, although retained longer, the insoluble precipitate will be removed. It cannot be determined or predicted from the information in the specification or in the art of record that the invention will function as claimed."

Response (g'):

While it is true that the extra-cellular precipitate of the present invention will eventually be removed by phagocytosis or convective flow, it need remain in the extra-cellular fluid of the cancer only for a matter of days in order for the present invention to be practiced.

One of skill in the art would be aware of the extensive publications studying the vasculature and growth of tumors, especially those referenced in the specification (page 35-36), and the Publication Exhibits showing the absence of lymphatic drainage and the inhibition of macrophages in the tumor (Publication Exhibits B and C, page 36 submitted with the response filed May 25, 1999). The literature cited in the present invention provides sufficient guidance to enable one skilled in the art to successfully predict, without undue experimentation, that the radio-labeled therapeutic agent will function as disclosed in the present invention, and that the

extra-cellular radio-labeled precipitate will remain in the tumor tissue longer than normal tissue (i.e. will be removed from tumor tissue much more slowly), and furthermore that the extra-cellular radio-labeled precipitate will remain in the tumor tissue for sufficient time for the present invention to be practiced.

For example, trypan blue adsorbed to albumin (a soluble macromolecule) is retained in tumor tissue for over 5 days, whereas it remains in normal tissue for only a few hours – this difference reflects the fact that normal tissues, but not cancer tissues, have an effective lymphatic drainage. Those skilled in the art would understand that this difference (days in cancer tissues versus hours in normal tissues) would be amplified for insoluble materials. This is confirmed by the long-term retention of insoluble DNA which has been relocated from inside cells to the extra-cellular fluid.

See also Mayers Declaration of January 2, 2003.

Paper 40, Page 4, Line 1-3, (e'), (g'), (h')

"...(e'), (g'), (h') the arguments are not persuasive for the reasons previously set forth in Papers Nos. 15 and 27."

Paper 18, Page 3, Line 10-13, (h)

"...(h) The making of soluble precipitable material is disclosed ... "

Paper 18, Page 5, Line 9, (h')

"...(h') The argument is not persuasive for the reasons previously disclosed"

Response (h'):

See response (a'), (b'), and (c').

See also Mayers Declaration of January 2, 2003.

In addition, there is attached the letter of Mr. George L. Mayers, executed on January 2, 2003, which is in support of the patentability of the invention of the application in view of the Official Action, Paper No. 40, mailed July 5, 2002.

Favorable action is solicited.

Respectfully submitted,

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